GRAS ASSOCIATES, LLC
20482 Jacklight Lane
Bend, OR 97702-3074
541-678-5522
mcquate@gras-associates.com

September 26, 2011

Food and Drug Administration
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety (HFS-255)
5100 Paint Branch Parkway
College Park, MD 20740-3835

Attention: Dr. Mary D. Ditto

Re: GRAS Notification – Salona™ Low Sodium Sea Salt

Dear Dr. Ditto:

On behalf of St. Louis-based ICL Performance Products LP, we are submitting for FDA review a GRAS notification for Salona™ Low Sodium Sea Salt. The attached documentation contains the specific information that addresses the safe human food uses for the subject notified substance. Four copies of the subject document are provided since meat and poultry product applications are anticipated for the notified substance which would require coordinated review with USDA.

If additional information or clarification is needed as you and your colleagues proceed with the review, please feel free to contact me *via* telephone or email.

We look forward to your feedback.

Sincerely,

(b) (6)

Robert S. McQuate, Ph.D.
CEO & Co-Founder
GRAS Associates, LLC
20482 Jacklight Lane
Bend, OR 97702-3074
541-678-5522
rmcquate@gras-associates.com
www.gras-associates.com

Enclosure: GRAS Notification for Low Sodium Sea Salt (4 copies)

000002

GRAS ASSOCIATES, LLC

GRAS ASSESSMENT

of

Salona™ Low Sodium Sea Salt

Food Usage Conditions for General Recognition of Safety

For

ICL Performance Products LP
St. Louis, MO

Evaluation By

Richard C. Kraska, Ph.D., DABT
Robert S. McQuate, Ph.D.
Madhusudan G. Soni, Ph.D., FACN

September 23, 2011

TABLE OF CONTENTS

TABLE OF CONTENTS continued

TABLE OF CONTENTS continued

FIGURES

TABLES

I. GRAS EXEMPTION CLAIM

A. Claim of Exemption from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR 170.36(c)(1)[1]

ICL Performance Products LP ("ICL") has determined that its low sodium sea salt product---referred to as Salona™ Low Sodium Sea Salt---which meets the specifications as described below---is Generally Recognized As Safe (GRAS) in accordance with Section 201(s) of the Federal Food, Drug, and Cosmetic Act. This determination was made in concert with an appropriately convened panel of experts who are qualified by scientific training and experience. The GRAS determination is based on scientific procedures as described in the following sections. The evaluation accurately reflects the conditions of the intended uses of this ingredient in foods.

Signed:

(b) (6)

September 26, 2011

Robert S. McQuate, Ph.D.
GRAS Associates, LLC
20482 Jacklight Lane
Bend, OR 97702-3074

Date

B. Name & Address of Notifier

ICL Performance Products LP
622 Emerson Road, Suite 500
St. Louis, MO 63141

As the notifier, ICL accepts responsibility for the GRAS determination that has been made for Salona™ Low Sodium Sea Salt and as described in the subject notification. Consequently, the Salona™ preparations meeting the conditions described herein are exempt from premarket approval requirements for food ingredients.

C. Common Name & Identity of the Notified Substance

The common name of the notified substance is potassium magnesium chloride hydrate, or alternatively, magnesium potassium chloride hydrate. This salt is a mineral (carnallite) that is

[1] See 62 FR 18938 (17 April 1997) which is accessible at http://www.gpo.gov/fdsys/pkg/FR-1997-04-17/pdf/97-9706.pdf#page=1.

found in the sea water of the Dead Sea in Israel. After harvesting, washing, and drying this sea salt, it is in a purified form containing a substantially reduced level of sodium chloride (halite) from the sea water. The notified substance trade name is Salona™ Low Sodium Sea Salt.

D. Conditions of Intended Use in Food

Salona™ preparations are intended to be used as a substitute for a portion of the sodium chloride (common table salt) used in various food categories including meat and poultry products at per serving levels that reflect good manufacturing practices in that the quantities added to foods should not exceed the respective amounts reasonably required to accomplish its intended technical effect.

E. Basis for the GRAS Determination

Pursuant to 21 CFR 170.30, Salona™ has been determined to be GRAS on the basis of scientific procedures as discussed in the detailed description provided below. In addition, dominant component salts found in Salona™---potassium chloride and magnesium chloride---have been previously affirmed as GRAS (21 CFR 184.1622 and 21 CFR 184.1426, respectively) and sodium chloride has historically been considered to be GRAS (see Section II.D.2 for more detailed regulatory background on sodium chloride). A comprehensive literature search conducted through June 22, 2011 was used for this safety evaluation.

F. Availability of Information

The data and information that serve the basis for this GRAS notification will be sent to the US Food and Drug Administration (FDA) upon request or will be available for review and copying at reasonable times at the offices of GRAS Associates, LLC, located at 20482 Jacklight Lane, Bend, OR 97702-3074.

II. INTRODUCTION

A. Objective

At the request of ICL, GRAS Associates, LLC ("GA") has undertaken an independent safety evaluation of Salona™ for use as a substance added to foods. The purpose of the evaluation is to ascertain whether or not the intended food uses of Salona™ can be considered to be Generally Recognized As Safe (GRAS) when used in various food products for intended technical effects that include, but are not limited to: flavor enhancer as defined by 21 CFR 170.3(o)(11); flavoring agent as defined by 21 CFR 170.3(o)(12); nutrient as defined by 21 CFR 170.3(o)(20); stabilizer and thickener as defined by 21 CFR 170.3(o)(28); and color-retention agent as defined by 21 CFR 170.3(o)(4) in various food products.

B. Foreword

ICL provided background information needed to enable the subject GRAS assessment to be undertaken. In particular, the information that was provided addressed the safety/toxicity of Salona™ and its components; the intended food uses; and compositional details, specifications, and method of preparation. ICL was asked to include adverse reports, as well as those that support conclusions of safety. Safety/toxicity studies performed with animals were noted to have value, along with available human testing. Determining how much Salona™ is to be consumed, i.e., the use levels, is critical in the determination of safe exposure levels for Salona™ when consumed as a food ingredient. The composite safety/toxicity studies, in concert with exposure information, ultimately provide the specific scientific foundation for the GRAS evaluation.

The safety/toxicity studies, consumption/exposure information, and other related documentation was augmented with an independent search of the scientific and regulatory literature up to August 31, 2011. Based upon the composite information, a GRAS assessment based primarily on available safety information with corroborative information based on common occurrence in food was undertaken. Those references that were deemed pertinent to the objective at hand are listed in Section VIII.

C. FDA Regulatory Framework

Ingredients for use in foods must undergo premarket approval by FDA as food additives or, alternatively, the ingredients to be incorporated into foods must be determined to be generally recognized as safe (GRAS). The authority to make GRAS determinations is not restricted to FDA. In fact, GRAS determinations may be provided by experts who are qualified by scientific training and experience to evaluate the safety of food and food ingredients under the intended conditions of use.

In 1997, FDA altered the GRAS determination process by eliminating the formal GRAS petitioning process and replacing the petitioning process with a notification procedure. While

outlining the necessary content to be considered in making a GRAS determination, FDA encouraged that such determinations be provided to FDA in the form of a notification. However, notifying FDA of such determinations is strictly voluntary.

D. Regulatory History of Potassium Chloride (KCl), Magnesium Chloride ($MgCl_2$) & Sodium Chloride (NaCl)

Salona™ Low Sodium Sea Salt is a natural mineral consisting of hydrated potassium magnesium chloride [$KMgCl_3 \cdot 6(H_20)$], also known as carnallite. Its mineral structure includes potassium chloride (KCl) and magnesium chloride ($MgCl_2$). In addition, a low level (less than 7%) of sodium chloride (NaCl) is co-evaporated from the sea water source of this mineral.

1. Magnesium Chloride & Potassium Chloride

The major constituents of Salona™ are potassium chloride (KCl) and magnesium chloride ($MgCl_2$), which are both currently affirmed as GRAS by the FDA as found in 21 CFR 184.1622 and 21 CFR 184.1426, respectively. Both ingredients must meet the specifications of the Food Chemicals Codex and must be produced in accordance with current good manufacturing practices (GMPs). GMPs for KCl specify that it may be used as a flavor enhancer, a flavoring agent, a nutrient supplement, a pH control agent, and a stabilizer or thickener. GMPs for $MgCl_2$ specify that it may be used as a flavoring agent, an adjuvant and a nutrient supplement.

The Joint FAO/WHO Expert Committee of Food Additives (JECFA) has also published specifications for both KCl and $MgCl_2$ (JECFA, 2006). Key JECFA specifications for the two compounds are as follows:

Chemical Name:	**Potassium Chloride**
Assay:	Not less than 99.0% on the dried basis
Functional Uses:	Seasoning agent, gelling agent, yeast food
Loss on Drying:	Not more than 1%
Iodide or Bromide:	Dissolve 2 g of the sample in 6 mL of water, add 1 mL of chloroform, and then add, drop wise and with constant agitation, 5 mL of a mixture of equal parts TS and water. The chloroform is free from even a transient violet or permanent orange color.
Test for Sodium:	Negative
Lead:	Not more than 2 mg/kg

Chemical Name:	**Magnesium chloride hexahydrate**
Assay:	Not less than 99.0% and not more than 105.0%
Functional Uses:	Firming agent, color retention agent
Ammonium:	Not more than 50 mg/kg
Lead:	Not more than 2 mg/kg

The current Food Chemicals Codex (FCC, 7th edition) includes specifications on both KCl and $MgCl_2$. Key specifications for the two compounds are as follows:

Chemical Name:	**Potassium Chloride**
Assay:	Not less than 99.0% on the dried basis
Loss on Drying:	Not more than 1.0%
Iodide or Bromide:	Dissolve 2 g of the sample in 6 mL of water, add 1 mL of chloroform, and then add, drop wise and with constant agitation, 5 mL of a mixture of equal parts of chlorine TS and water. The chloroform is free from even a transient violet or permanent orange color.
Test for Sodium:	Not more than 0.5%
Heavy Metals (as Pb):	Not more than 5 mg/kg

Chemical Name:	**Magnesium chloride**
Assay:	Not less than 99.0% and not more than 105.0% of $MgCl_2 \cdot 6H_2O$
Ammonium:	Not more than 0.005%
Lead:	Not more than 4 mg/kg
Sulfate:	No more than 0.03%

The Select Committee on GRAS Substances also reviewed KCl and $MgCl_2$ for FDA (SCOGS, 1976, 1979) and concluded that there is no evidence in the available information on KCl or $MgCl_2$ that demonstrates or suggests reasonable grounds to suspect a hazard to the public when they are used at levels that are now current and in the manner now practiced, or which might reasonably be expected in the future.

2. Sodium Chloride

The regulatory history of salt (sodium chloride, NaCl) is more complex. The Institute of Medicine's Committee on Strategies to Reduce Sodium Intake (IOM, 2010) has reviewed the regulatory history of NaCl in depth. In 1959, when FDA issued its original GRAS list, the agency said that it is "impracticable" to list all GRAS substances, and it named salt (along with pepper, vinegar, baking powder and monosodium glutamate) as examples of common food substances that it considered to be safe and, thus, presumably GRAS. To this day, salt is still only listed as an example of a GRAS substance in 21 CFR 182.1 and is not listed on the formal GRAS list for use as a direct food ingredient. However, NaCl is specifically listed as a GRAS substance that migrates to food from paper and paperboard products and cotton and cotton fabrics used in food packaging (21 CFR 182.70, 21CFR 182.90).

In response to a 1969 White House directive, the GRAS ingredient reviews were conducted by FDA in concert with the SCOGS. In 1979, SCOGS delivered its safety review on sodium chloride and concluded that the evidence on sodium chloride was "insufficient to determine that the adverse effects reported are not deleterious to the health of a significant proportion of the public when it is used at levels that are now current and in the manner now practiced." This conclusion on salt is of the type, under the GRAS Review Program, that would normally trigger FDA action to revise or revoke the GRAS status of a substance and, at a minimum, would raise

concerns about the GRAS status of added salt in light of the "reasonable certainty of no harm safety" standard and the requirement that there be "general recognition" of safety to achieve and maintain GRAS status.

In early 1978, FDA was petitioned to reclassify salt from a GRAS substance to a food additive, which would make salt subject to premarket approval for its use. In addition, the petitions encouraged FDA to implement other aspects of existing regulations and require a warning label on high-sodium foods and salt packets. The petitions did not request that FDA modify the conditions under which salt could be used in foods as a GRAS substance---only that salt no longer be classified as GRAS.

In 1982, based on the SCOGS report and its own analysis of its regulatory options, FDA published a "Policy Notice" in which it called for reductions in the levels of added salt in processed foods based on concerns about hypertension but further concluded that it would not act "at this time" to revise the GRAS status of salt, relying instead on public education, voluntary industry efforts, and a new FDA effort to expand disclosure of sodium content on product labels. In the 1982 notice, FDA said: "The agency wishes to emphasize that if there is no substantial reduction in the sodium content of processed foods and if information [sic] sodium labeling is not adopted after a reasonable period, FDA will consider additional regulatory actions, including proposing a change in salt's GRAS status."[2]

In 2005, the House of Representatives' Committee on Appropriations issued a statement that encouraged the Secretary of Health and Human Services "to focus on ways—including both voluntary actions by the food industry and regulatory actions by FDA and the Department of Agriculture—to reduce salt in processed and restaurant foods."[3] A citizen petition submitted to FDA by the Center for Science in the Public Interest (CSPI) in 2005 cited, among other reports, the congressional committee's statement and requested FDA to (1) revoke the GRAS status of salt, (2) amend any prior sanctions for salt, (3) require food manufacturers to reduce the amount of sodium in all processed foods, (4) require health messages on retail packages of salt (≥ 0.5 oz), and (5) reduce the Daily Value (DV) for sodium from its current level of 2,400 mg to 1,500 mg. In response to the petition, FDA held a public hearing in November 2007 to discuss the regulatory status of salt. The comment period for additional responses to the public hearing and the petition closed in August 2008. To date, no further FDA action on this petition has taken place.

[2] See 47 Federal Register 26593 (1982).
[3] H.R. Rept. 109-143. 109th Congress, 1st session. (June 21, 2005) at 142.

III. INGREDIENT IDENTITY, CHEMICAL CHARACTERIZATION, MANUFACTURING PROCESS & PURITY

Salona™ is a trade name for ICL's low sodium salt substitute. It is a natural mineral consisting of hydrated potassium magnesium chloride [$KMgCl_3 \cdot 6(H_20)$] and is also known as carnallite. While it can be found as an evaporite mineral in some marine salt deposits, ICL produces a high-purity version of this double chloride mineral by extracting it directly from sea water in the Dead Sea in Israel.

Salona™ is produced by evaporation of sea water from the Dead Sea through a series of evaporation ponds in which most of the sodium chloride (NaCl) is precipitated. The leftover brine is further concentrated, and the potassium magnesium chloride hydrate mineral crystallizes and precipitates. This precipitated mineral is mechanically "harvested" from the bottom of the pools and pumped through pipes to the plant where the potassium magnesium chloride sea salt crystals are separated from the solution, washed, and dried.

A. Chemical Identity of Salona™ Low Sodium Sea Salt

1. Common or Usual Name

The common or usual names of the mineral product that is the subject of the GRAS evaluation are: potassium magnesium chloride hydrate, or alternatively, magnesium potassium chloride hydrate. The specific substance that is the subject of this safety evaluation is identified by the trade name Salona™ or Salona™ Low Sodium Sea Salt, as produced and sold by ICL. The compositional features of the subject low sodium sea salt are described in more detail below.

2. Trade Name

Salona™ Low Sodium Sea Salt is a trade name for a low sodium salt substitute that is extracted from sea water and consists of a mineral that contains primarily potassium, magnesium, and chloride.[4]

3. Formal Names (IUPAC or Chemical Abstracts Name)

Potassium magnesium chloride hydrate

4. Synonyms, Other Common Names, Trade Names

Hydrated Potassium Magnesium Chloride
Salona™
Salona™ Low Sodium Sea Salt
Low Sodium Maris Sal
Carnallite

[4] The description of Salona™ as a low sodium sea salt is used to distinguish it from other sea salt products which typically are predominantly sodium chloride and, therefore, contain significantly higher levels of sodium. The incorporation of Salona into processed foods will facilitate the production of foods that may qualify as "low sodium" foods, "reduced sodium" foods, or other appropriately descriptive terms as allowed by 21 CFR 101.61. Also see Section IV.A.

5. Chemical Formulas

Representative empirical formulas for the ingredient include:

$KMgCl_3 \cdot 6H_2O$
$KCl\ MgCl_2 \cdot 6H_2O$

6. Molecular Weight

277.85

7. Chemical Abstracts Service Registry Number (CAS Registry No.)

107762-48-1

8. Characteristic Properties

Appearance:	White to off-white crystalline solid
Taste:	Salty
Odor:	Odorless
Solubility:	Very soluble in water

9. Chemical Composition

Salona™ is a water-soluble low sodium sea salt with a molecular formula of $KClMgCl_2 \cdot 6H_20$. The typical composition of Salona™ is given in Table 1.

B. Source Material of Salona™ Low Sodium Sea Salt

Carnallite, the source material for Salona™, is an evaporite mineral---hydrated potassium magnesium chloride. Halite (NaCl), small quantities of sylvite (KCl), and impurities of water-insoluble clay-like and carbonate minerals can be found in naturally-occurring deposits of carnallite. The Salona™ is produced by evaporation of sea water from the Dead Sea. Salona™ is the only known sea water-derived source of carnallite. Other "deposits" of carnallite, which must be mined, have lower purity due to co-deposition with other minerals and substances.

C. Manufacturing Process for Salona™ Low Sodium Sea Salt

Salona™, or Salona™ Low Sodium Sea Salt, is a natural sea salt that is harvested from the sea water of the Dead Sea in Israel by a business unit of Israel Chemicals Limited (ICL) called the Dead Sea Works (DSW). Solar energy is utilized to extract minerals from one of the largest solar evaporation pond arrays in the world. The ICL facilities on the Dead Sea use processes and technology similar to that used to harvest sea salt from solar evaporation ponds near the oceans and other salt water bodies around the world.

Table 1. Typical Composition of Salona™ Low Sodium Sea Salt

COMPOSITION	Typical values	METHOD
Magnesium chloride ($MgCl_2$)	31-35%	EDTA Titration
Potassium chloride (KCl)	21-26%	Atomic Absorption
Sodium chloride (NaCl)	7% maximum	Atomic Absorption
Bromide (Br)	0.4% maximum	Iodometric
Aluminum (Al)	1 ppm	ICP-OES
Boron (B)	3 ppm	ICP-OES
Iron (Fe)	2 ppm	ICP-OES
Manganese (Mn)	1 ppm	ICP-OES
Silicon (Si)	5 ppm	ICP-OES
Strontium (Sr)	8 ppm	ICP-OES
Ammonia	0.07%	Ion Chromatography
Calcium	0.1%	EDTA Titration
Sulfates	150 ppm	Gravimetric

The production process is based on precipitation of the minerals on the bottom of man-made evaporation ponds, dredging the minerals by large, auger-style dredges, and processing it into final products. For the construction of the ponds, a system of dams was built, which today encompasses much of the Israeli sector of the shallow southern basin of the sea. This creates a series of evaporation ponds. An essential part of the process is minimizing the precipitation of table salt (NaCl) in the last of the evaporation ponds where the Salona™ is retrieved. Therefore, in the first phase of processing, the water of the Dead Sea is pumped from the deep northern basin *via* canal to the southern basin into ponds to precipitate most of the NaCl.

In the initial ponds, natural evaporation results in about a 50% reduction in its initial volume so that the sodium salt crystallizes out. The brine, with a minimal content of NaCl, is pumped into the final production ponds. In these ponds the remaining solution is further concentrated, and the potassium magnesium chloride hexahydrate crystallizes and precipitates. This material is mechanically "harvested" from the bottom of the ponds and pumped through pipes to the plant, where these mineral crystals are separated from the solution. The production of Salona™ involves transferring these damp crystals to the food grade salt plant where they are washed, dried, sized and packaged. This process results in a white to off-white product which assures the limitation of trace minerals. The flow chart found in Figure 1 summarizes the production process that yields Salona™ Low Sodium Sea Salt.

D. Quality Control of Manufacturing Process

The overall facility in Israel, where Salona™ Low Sodium Sea Salt is dried, sized, and packaged, also produces other food grade salts for the global food industry. It utilizes a HACCP program, has standardized internal quality audits, operates under Good Manufacturing Practices, and is licensed by the Israel Ministry of Health. The new section of this facility for Salona packaging is progressing toward these same standards, which will be completed in the near future. Until the implementation and verification of these standards are completed, the final product packaging step (including HACCP metal detection, repacking into food grade bags, and finished product label control) will be completed at a food grade contract facility in the US.

E. Product Specifications

1. General Physical Properties

Salona™ Low Sodium Sea Salt is a white/off-white granular crystal with a characteristic saline taste without any odor. Its primary use is as a low sodium salt substitute to reduce levels of sodium in foods.

2. Physical/Chemical Specifications

The physical properties and specifications for Salona™ low sodium sea salt are compiled in Table 2. Information is provided in Appendix A from nine Certificates of Analysis demonstrating that these production batches of Salona™ all meet the physical and chemical specifications.

3. Contaminants

The typical levels found for possible contaminants for Salona™ are listed in Table 3.

4. Microbiological Content

An inorganic compound such as Salona™ will typically not support microbiological growth and, therefore, microbiological parameters are not routinely reported or tested. Several lots of Salona have been submitted for microbiological analysis, and there was no detection (Detection Limit < 10 colony-forming units) in any samples for either the Aerobic Plate Count test or the Yeast & Mold test.

5. Nutrition Content

A typical nutritional analysis of Salona™ is given in Table 4.

Figure 1. Flow Chart for the Manufacturing Process of Salona™ Low Sodium Sea Salt

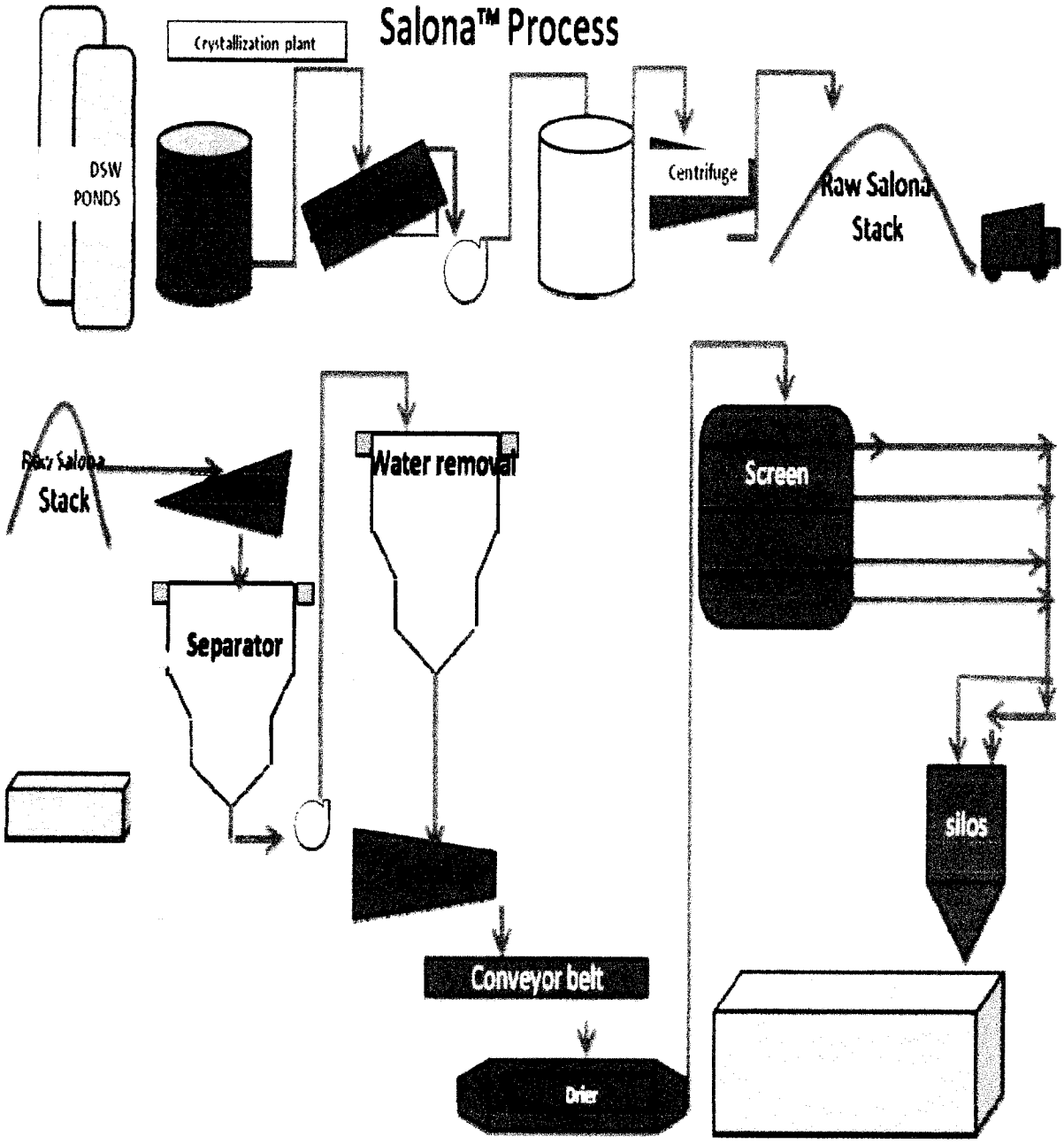

Table 2. Salona™ Low Sodium Sea Salt Physical & Chemical Specifications

Organoleptic Properties	Description
Physical form	Granular crystal
Color	White to Off-white
Flavor	Saline
Odor	Odorless
Chemical & Physical Data	**Specification Limits**
Magnesium Chloride ($MgCl_2$)	31%-35%
Potassium Chloride (KCl)	21%-26%
Sodium Chloride (NaCl)	7% Maximum
Bromide (Br)	0.4% Maximum
Total Organic Carbon	10 ppm Maximum
Lead (Pb)	2 ppm Maximum
Heavy Metals (as lead)	10 ppm Maximum Includes Ag, As, Bi, Cd, Cu, Hg, Pb, Sb, Sn or other impurities colored by the sulfide ion
Water Insolubles	0.1% Maximum
Sizing, USSS – Fine Sizing, USSS – Medium Sizing, USSS – Coarse	15% Maximum, Retained on 20 mesh 10% Maximum, Retained on 12 mesh 90% Minimum, Retained on a 16 mesh

F. Stability Data

Salona™ Low Sodium Sea Salt is an inorganic compound that exists in a stable mineral form. No chemical reactions are anticipated to occur under normal conditions of storage and handling. If heated above the decomposition temperature (160°C), some HCl could form. Salona has the potential to be slightly hygroscopic. To improve caking resistance, Salona should be stored in a dry covered area at humidity below 75%. The shelf-life of Salona has been estimated to be 60 months.

Table 3. Typical Contaminant Analysis of Salona™ Low Sodium Sea Salt

PESTICIDES		
PESTICIDE	TYPICAL	METHOD
Organo Halogens	Non Detectable (<0.2 ppm)	AOAC 2007.01
Organo Nitrogen	Non Detectable (<0.1 ppm)	AOAC 2007.01
Organo Phosphates	Non Detectable (<0.05 ppm)	AOAC 2007.01
N-Methyl Carbamates	Non Detectable (<0.1 ppm)	AOAC 2007.01
OTHER CONTAMINANTS		
CONTAMINANT	TYPICAL	METHOD
Bromide	0.4% Maximum	Iodometric
Perchlorates	Non Detectable (<0.002 ppm)	HPLC / MS
Mercury	Non Detectable (<0.05 ppm)	ICP-OES
Lead	2 ppm Maximum	ICP-OES
Total Heavy Metals (as lead)	10 ppm Maximum	Sulfide
Arsenic	Non Detectable (<1 ppm)	ICP-OES
Nitrate (as nitrogen)	< 8 ppm	Colorimetric
Nitrite (as nitrogen)	< 2 ppm	Colorimetric
Total Organic Carbon	10 ppm Maximum	UV-IR

Table 4. Nutrient Composition of Salona™ Low Sodium Sea Salt

NUTRIENT/COMPONENT	TYPICAL VALUES PER 100 G
Calories	0
Protein	0
Carbohydrates	0
Fat	0
Ash[a]	62 g
Moisture (Loss on Drying)[b]	< 1 g
Potassium	12.5 g
Magnesium	8.5 g
Calcium	0.1 g
Sodium	1.7 g

[a] Calculated value. The balance of the product is water of hydration.
[b] Test conditions: 80°C under vacuum (<20 mm Hg) for 4 hours.

IV. INTENDED USE & DIETARY EXPOSURE

A. Intended Use

Salona™ is a highly purified, food grade sea salt intended to be used as a salt (NaCl) substitute in foods including meat and poultry products. However, because of palatability issues when used alone or as a substitute for a high proportion of the regular salt content of foods, Salona™ is not expected to be a 100% replacement for sodium chloride. The addition of Salona™ to food allows manufacturers and consumers to add less sodium chloride to food without substantially reducing the salty taste of foods. The intended use levels will vary by actual food category, but the actual levels are self-limiting due to organoleptic factors and consumer taste considerations. However, the amounts of Salona™ to be added to foods will not exceed the amounts reasonably required to accomplish its intended technical effect in foods as required by FDA regulation.[5]

Food applications which have been successfully tested with partial replacement of NaCl with Salona™ include: crackers, biscuits, cakes, breads, and tortillas; cheese and enchilada sauces; meatballs, chicken and pork sausages; taco-seasoned beef; chicken broth; tomato juice; and French fries and chocolate-covered caramels (topical application). Additional potential applications for Salona™ are anticipated in the following types of foods: baked goods; cereal / grain foods; snacks; soups; fish products; frozen foods; meat products; cheese and other dairy goods; spices and seasonings; beverages; ready to eat meals and virtually any food and beverage products which contain salt.

It is anticipated that Salona™ will be utilized by both food manufacturers and individual consumers. The manufacturers are expected to use Salona™ to reduce the sodium content of processed foods so that labeling claims such as "reduced or less sodium,"[6] "low sodium,"[7] or other approved sodium-related nutrient content claims (as described in 21 CFR 101.61) may be utilized . It is also anticipated that salt blends containing both sodium chloride and Salona™ may be used by health-conscious consumers who wish to lower their sodium intake during food preparation and at the table to season foods.

The sole use of Salona™ is as a replacement for a portion of the sodium chloride in the diet. Therefore, potential exposure to Salona™ may be estimated using current data on sodium consumption data by the US population.

---

[5] See 21 CFR 182.1(b)(1).
[6] At least 25% less sodium per reference amount than an appropriate reference food as described in 21 CFR 101.61(b)(6).
[7] 140 mg of sodium or less per reference amount as per 21 CFR 101.61(b)(4).

B. Dietary Exposure

Based on the intended food uses of Salona™ as a salt substitute, a point estimate for dietary intake was calculated using the Dietary Guidelines for Americans 2010, USDA (released 1/31/2011).[8] The estimated average intake of sodium (from all foods with the exception of discretionary table salt) for all Americans ages 2 years and older is approximately 3.4 g/person/day. Assuming 100% of the 3.4 grams per day of elemental sodium is in the form of sodium chloride (table salt), the average intake of sodium chloride is 8.5 grams/day (sodium chloride is 40% sodium). Using FDA's assumptions of twice the average for estimating the consumption by a high user at the 90th percentile consumption level, the high user consumption level of sodium chloride is estimated to be 17 g/person/day.

There are numerous adjustments to this estimate that need to be made to more accurately reflect the potential dietary exposure to Salona™. First, this estimate does not include sodium chloride from discretionary use of table salt. Mattes and Donnelly (1991) reported that discretionary table salt use (both table salt and cooking salt) accounts for about 11% of dietary sodium intake. If the daily sodium chloride intake estimate is increased by 11% to account for use of table salt, the estimated level for the 90th percentile consumption levels would increase to 18.9 g/person/day.

Second, these estimates include both sodium added to foods in processing (from all sources, including food additives such as monosodium glutamate, sodium alginate, sodium benzoate, baking soda, baking powder, sodium phosphate and/or sodium nitrate) plus sodium naturally present in foods. According to Mattes and Donnelly (1991), sodium added during processing of foods contributes 77% of total intake, while on average, the natural sodium content of food accounts for 12% of total intake. Therefore, another adjustment must be made to reflect the fact that the 12% of sodium found inherently in foods cannot be substituted with Salona™. Reducing the 18.9 g/person/day estimate by 12% brings the estimated dietary intake to 16.6 g/person/day.

Lastly, Salona™ is not expected to replace 100% of the sodium added to foods due to palatability issues. The anticipated use rate for reducing the Na level in the foods is up to 25% replacement of NaCl with Salona™. Therefore, final estimates for the 90th percentile consumption levels based on a 25% replacement of sodium chloride in processed foods, as well as table salt and cooking salt, is 4.15 g/person/day of Salona™, if all of the sodium consumed is from added sodium chloride.

The typical nutritional component analysis for individual minerals, such as K, Mg, Na and Br in Salona™, is presented in Table 4. Table 5 shows the calculations for estimation of K, Mg, Na and Br ions based on consumption for a high user of salt whose food choices had Salona™ substituted for 25% of its sodium chloride (with the assumption that all sodium in the food is from sodium chloride).

[8] Available at http://www.cnpp.usda.gov/Publications/DietaryGuidelines/2010/DGAC/Report/2010DGACReport-camera-ready-Jan11-11.pdf.

Table 5. Estimated Daily Intake of K, Mg, Na & Br from Salona™ Low Sodium Sea Salt Substitution

SALONA™ COMPONENT	ESTIMATED INTAKE BASED ON 4.15 G/PERSON/DAY
Potassium (K)	457-565 mg/day
Magnesium (Mg)	319-360 mg/day
Sodium (Na)	116 mg/day
Bromide (Br)	17 mg/day

V. REVIEW OF SAFETY DATA

As discussed in Sections II.D and III.A, the main components of Salona™---potassium chloride, magnesium chloride and sodium chloride---are already considered to be GRAS for their intended food uses. Therefore, this section will only briefly discuss the safety of these principal components, followed by a more detailed discussion of the concerns associated with the safety of bromide. While bromide is not part of the mineral form of Salona, due to the source of this sea salt, it could be present in Salona at levels not more than 0.4% bromide.

In the published literature, several studies are available on the biological and toxicological effects of the components of Salona™. As the mineral constituents of Salona™ are essential for human nutrition and are commonly ingested, these constituents have been frequently and extensively reviewed for their safety by national and international regulatory agencies and organizations including the Food and Nutrition Board of the Institute of Medicine (IOM) of the National Academy of Sciences, Food and Drug Administration (FDA), and the World Health Organization (WHO). For the purpose of the safety assessment of Salona™ constituents, reports from these agencies were considered. Additional recent safety/toxicity studies were also reviewed for each of the ingredients. However, the depth of review was based on the estimated intake levels of constituents resulting from the use of Salona™ compared to the recommended daily allowance and/or the tolerable upper intake of these ingredients.

A. Potassium Chloride (KCl)

1. Dietary Intake

The IOM Panel in the publication entitled The Dietary Reference Intakes for Water, Potassium, Sodium Chloride and Sulfate (IOM, 2005) reported that the median intake of potassium by adults in the United States was approximately 2.9 to 3.2 g/day for men and 2.1 to 2.3 g/day for women.

2. Summary of Opinions in the Scientific & Medical Community about Safety of Potassium Chloride

As mentioned in Section II.D, KCl is affirmed as GRAS by FDA for its intended uses as a flavor enhancer, a flavoring agent, a nutrient supplement, a pH control agent, and a stabilizer or thickener. The SCOGS (Select Committee on GRAS Substances) opinion (1979) states that potassium chloride is an essential constituent of the body and is rapidly adjusted to homeostatic levels following ingestion in amounts that can be tolerated without causing nausea and vomiting. When the SCOGS reviewed potassium chloride, the amount of potassium chloride added to food by processors in 1975 was on the order of 20 mg daily on a per capita basis while the amount of potassium in the average diet was equivalent to 4 to 9 g of potassium chloride. The Committee reports that serious toxic reactions to potassium chloride rarely occur. An occasional complication from concentrated potassium chloride tablets given orally is ulceration of the small intestine. At the time of the review, the available evidence indicated that in normal

individuals potassium chloride is well tolerated and that metabolism quickly and efficiently adjusts potassium in the body to narrow homeostatic levels.

The Committee also notes that potassium chloride could be substituted for sodium chloride in some of its applications but that the unpleasant taste of substantial amounts of potassium chloride, in the absence of sodium chloride, makes this improbable. Thus, the Select Committee believed that the extensive substitution of potassium chloride, which might increase its per capita usage from 20 mg to 2 g or more, is unlikely. If this degree of substitution were made, the ratio of sodium to potassium in the diet would be reduced from the current value of approximately 1.4 to a value nearer 0.9 in a 2600 kcal diet which would provide about 160 mg potassium and 140 mg sodium per 100 kcal. By replacing some sodium containing ingredients with ingredients that provide other cations and by increasing the consumption of foods lower in sodium content, it is probable that reduced sodium intakes would be a more important factor than increased consumption of potassium in lowering this ratio. In the final opinion, the Committee concluded that there is no evidence in the available information on KCl that demonstrates or suggests reasonable grounds to suspect a hazard to the public when they are used at levels that are now current and in the manner now practiced, or which might reasonably be expected in the future.

The IOM Panel (IOM, 2005) has set 4700 mg potassium/day as an Adequate Intake (AI) for all adults. In its report the Panel indicated that intake of potassium at this level from foods should maintain lower blood pressure levels, reduce the adverse effects of sodium chloride intake on blood pressure, reduce the risk of recurrent kidney stones, and possibly decrease bone loss. Because of lack of sufficient data from dose-response trials demonstrating effects of potassium, the Panel could not establish an Estimated Average Requirement and thus could not set a Recommended Dietary Allowance (RDA) for potassium. The report suggests that at present, dietary intake of potassium by all groups in the United States and Canada is considerably lower than the AI. In the generally healthy population with normal kidney function, potassium intake from foods above the AI poses no potential for increased risk because excess potassium is readily excreted in the urine. Therefore, a Tolerable Upper Intake Level (UL) was not set.

B. Magnesium Chloride

1. Dietary Intake

Using data from the National Health and Nutrition Examination Survey 1999–2000, the Center for Disease Control (CDC) reports that the mean dietary intake of magnesium in the US was 290 mg/day (Ford and Mokdad, 2003). It was reported that a substantial number of US adults fail to consume the recommended dietary allowance of 310-420 mg magnesium (depending on gender) in their diets. This concurs with the SCOGS review which states that the usual adult intake of magnesium is about 300 mg or less per day from all sources, and the contribution of food additives to total magnesium intake is very small. The 1999–2000 NHANES survey indicates that a substantial number of US adults consume less than the recommended daily allowance of magnesium (King et al., 2005). Based on the NHANES survey, the daily average

intake of magnesium (including magnesium from dietary supplements) was 328 mg. Among US adults, 68% consumed less than the RDA of magnesium, and 45% consumed less than 75% of the RDA. This suggests that the current intake of magnesium is quite low.

2. Summary of Opinions in the Scientific & Medical Community about Safety of Magnesium Chloride

As previously discussed in Section II.D, $MgCl_2$ is affirmed as GRAS in 21 CFR 184.1426 for use as a flavoring agent, an adjuvant and a nutritional supplement. The SCOGS opinion for magnesium salts states that magnesium is a dietary essential that is involved in a myriad of metabolic reactions and is necessary for the activity of many intracellular enzymes. Magnesium salts along with certain other cations are also important in electrolyte balance. The Select Committee also states that The Food and Nutrition Board recommended that cereal grain products should be fortified with magnesium in view of the potential risk of deficiency among significant segments of the population.

The only mention of adverse effects for magnesium is in the case of magnesium sulfate which, at very high doses, occasionally has resulted in serious adverse events, especially in the presence of pre-existing disease. The committee states that these occurrences should not be prejudicial to the use of magnesium salts as food ingredients since the dosages given were orders of magnitude greater than the daily dietary intake of magnesium added to food.

The Select Committee also claims that while chronic toxicity data are lacking, the status of magnesium as a ubiquitous and essential dietary ingredient for the maintenance of homeostatic and bioenergetic mechanisms leads to the opinion that none of the available evidence suggests any probable hazard when any of the GRAS compounds of magnesium are used as a food ingredient. The Select Committee concluded that there is no evidence in the available information on magnesium carbonate, magnesium chloride, magnesium sulfate, magnesium hydroxide, magnesium oxide, magnesium stearate, dibasic magnesium phosphate and tribasic magnesium phosphate that demonstrates or suggests reasonable grounds to suspect a hazard to the public when they are used at levels that are now current and in the manner now practiced or which might reasonably be expected in the future.

The IOM Panel (IOM, 1997) has determined the upper tolerable limit for supplemental magnesium as 350 mg/day (calculated as elemental magnesium in the salt) for individuals 9 years and older. This limit was restricted, however, to magnesium obtained from dietary supplements, and no upper limit was set on intake of magnesium from food sources. According to the IOM report, magnesium, when ingested as a naturally occurring substance in foods, has not been demonstrated to exert any adverse effects. However, adverse effects of excess magnesium intake have been observed with intakes from nonfood sources such as various magnesium salts used for pharmacologic purposes. Thus, a Tolerable Upper Intake Level (UL) cannot be based on magnesium obtained from foods. All reports of adverse effects of excess magnesium intake concern magnesium taken in addition to that consumed from food sources. The primary adverse effects of excessive magnesium intake from nonfood sources are diarrhea. The diarrheal effect produced by pharmacological use of various magnesium salts is an osmotic effect and may be accompanied by other mild gastrointestinal effects such as nausea and

abdominal discomfort. Osmotic diarrhea has not been reported with normal dietary intakes of magnesium. Magnesium ingested as a component of food or food fortificants has not been reported to cause this mild, osmotic diarrhea even when large amounts are ingested.

Magnesium is absorbed much more efficiently from the normal concentrations found in the diet than it is from the higher doses found in nonfood sources. The presence of food likely counteracts the osmotic effect of the magnesium salts in the gut lumen. In normal individuals, the kidney seems to maintain magnesium homeostasis over a rather wide range of magnesium intakes. Thus, hypermagnesemia has not been documented following the intake of high levels of dietary magnesium in the absence of either intestinal or renal disease.

The IOM report includes the disclaimer that it is not known if all magnesium salts behave similarly in the induction of osmotic diarrhea. In the absence of evidence to the contrary, it seems prudent to assume that all dissociable magnesium salts share this property. Reports of diarrhea associated with magnesium frequently involve preparations that include aluminum, and therefore a specific magnesium-associated effect cannot be ascertained.

C. Sodium Chloride

1. Dietary Intake

Based on self-reported intake data in the US from the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994), the estimated median intake of sodium from foods (not including salt added at the table) varied by age group and ranged from 3.1 to 4.7 g (135 to 204 mmol)/day for men and 2.3 to 3.1 g (100 to 135 mmol)/day for women in the US. These intake ranges are equivalent to 7.8 to 11.8 g/day of sodium chloride for men and 5.8 to 7.8 g/day of sodium chloride for women.

2. Summary of Opinions in the Scientific & Medical Community about the Safety of Sodium Chloride

As discussed in Section II.D, while not specifically listed on the formal GRAS list for use as a direct food ingredient, except for its specific as a substance that migrates to food from paper and paperboard products and cotton and cotton fabrics used in food packaging (21 CFR 182.70, 21 CFR.182.90), sodium chloride (NaCl) has always been considered GRAS. SCOGS reported that sodium chloride is used as a direct food ingredient in 30 different processed food categories.

The SCOGS safety review reports that while sodium chloride is an essential constituent of the body and is present in many foods, it also exhibits acute and chronic toxic effects when ingested in excessive amounts. Excess sodium chloride may induce hypertension in rats. Hypertension has been evoked by excess sodium chloride in the food or drinking water of dogs, but the effects were reversible and related to osmotic factors. The causes of hypertension in man are related to genetic and environmental factors: race, family history, variations in endocrine and kidney function, degree of obesity, and lifestyle. Although the findings of epidemiological

studies suggest a relationship between salt intake and onset of hypertension, the evidence that salt consumption is a major factor in causing hypertension is not conclusive. However, available data suggest that 10 to 30 percent of the US population is genetically predisposed to hypertension and is exposed to a higher risk by ingestion of sodium chloride at current levels. The Select Committee believed that a reduction of sodium chloride consumption by the population would reduce the frequency of hypertension.

The SCOGS opinion also points out that the daily requirement of sodium chloride for humans is less than 1 g (17 mg/kg bw), and this amount is exceeded by the levels of NaCl present as a naturally-occurring ingredient of most diets. The Select Committee claimed it was not possible, on the basis of currently available data, to recommend a level of intake of sodium chloride that could be considered to be optimal for health. The SCOGS opinion concluded that the evidence on sodium chloride was insufficient to determine that the adverse effects reported are not deleterious to the health of a significant proportion of the public when it is used at levels that were current at the time. At the time of the report, such levels were reported to be about 180 mg/kg bw for an adult, or 10-12 grams per day. These levels exceed estimates of the amount (2-10 grams/day) that may elicit hypertension in susceptible individuals and recommends a lower daily consumption of sodium chloride for those individuals.

The IOM Panel (IOM, 2005) established a Tolerable Upper Intake Level (UL) for sodium chloride as 2.3 g sodium/day (5.8 g sodium chloride) based upon the increased risk of cardiovascular outcomes, particularly cardiovascular disease and stroke and the adverse effects of higher levels of sodium intake on blood pressure. The UL for sodium may well be lower among certain groups of individuals who are most sensitive to the blood pressure effects of increased sodium intake (e.g., older persons, African Americans, and individuals with hypertension, diabetes, or chronic kidney disease). In contrast, for individuals who are not acclimatized to prolonged physical activity in a hot environment, their needs may exceed the UL because of losses of sodium in sweat.

Based on the information from NHANES III, the IOM report (IOM, 2005) also concluded that more than 95 percent of men and 75 percent of women in the US had sodium intakes that exceeded the UL, even when the amount of sodium added to foods during meals (table salt) was excluded. In phase I of the same survey (NHANES III), 24.7 percent of men and 24.3 percent of women 18 years and older had hypertension—while a multifactoral diagnosis, hypertension is causally related to increased sodium intake. Therefore, the objective of the report was to recommend strategies for reducing sodium intakes to levels recommended by the Dietary Guidelines for Americans, which are to reduce the intake to less than 2,300 mg and further reduction to 1,500 mg among persons who are 51 and older, and those of any age who are African American or have hypertension, diabetes, or chronic kidney disease. The 1,500 mg recommendation applies to about half of the US population, including children and the majority of adults. The ultimate goal of the report's recommendations is to gradually, over time, reduce the sodium content of the food supply in a way that goes unnoticed by most consumers as individuals' taste sensors adjust to the lower levels of sodium.

D. Bromide Salts

1. General Description

Bromide (Br^-) is the anion of the element bromine (Br_2) that is a member of the common halogen element series that includes fluorine, chlorine, bromine and iodine. Free bromine does not occur in nature, but occurs as colorless soluble crystalline mineral bromide salts, such as sodium bromide (NaBr) and potassium bromide (KBr). These salts are found, although in smaller quantities, along with sodium chloride owing to their similar physical and chemical properties (Cotton and Wilkinson, 1962). The high solubility of bromide has caused its accumulation in the oceans, and commercially the element is easily extracted from brine pools, mostly in the US, Israel, and China. Bromide concentrations in seawater are generally in the range of 65 mg/L to well over 80 mg/L in some confined sea areas, compared with chloride which is present at 18,980 mg/L to over 23,000 mg/L (Al-Mutaz, 2000).

Potassium bromide (KBr) was widely used as an anticonvulsant and a sedative in the late 19th and early 20th centuries. Its action is due to the bromide (sodium bromide is equally effective) (Goodman, 1970). Potassium bromide is presently used as a veterinary drug as an antiepileptic medication for dogs and cats (EMEA (European Medicines Agency), 1997).

2. Dietary Intake

Although bromine has no essential role in human or mammalian health, the typical daily intake of bromide in the US is 2-8 mg from grains, nuts and fish (Nielsen, 1996).

3. Animal Studies

a. Absorption, Distribution & Excretion

Single doses of an aqueous solution of ^{82}Br-ammonium bromide were injected into tail veins of pregnant albino mice 2 days before parturition. The mice were euthanized at 5 min, 20 min, 1, 2, 4, 24 or 48 hrs, and the distribution of the ^{82}Br in the tissues of the dams and the fetuses was studied by autoradiography. The distribution of ^{82}Br was similar at the various time periods studied. The radioactivity was excreted slowly, which resulted in only slight decreases in concentration with increasing time periods. Blood levels remained high and exceeded those recorded for most organs and tissues. Bromide gradually accumulated in the central nervous system. The level in the thyroid was relatively high but did not exceed levels in the blood. Bromide showed transplacental passage, and most of the radioactive bromide was found in the bones of the fetuses, but the level was not as high as in the cartilage of the dams (Söremark & Ullberg, 1960).

Thirty females Wistar SPF rats received diets containing 2000 ppm sodium bromide for 3 weeks. Mean bromide concentration at the beginning of the bromide administration was 0.55 ± 0.46 mmol/L. After the 3 weeks of bromide administration, the bromide level reached 8.57 ± 0.57 mmol/L. The animals were then divided into 5 groups. Group 1 received a normal diet and tap water as drinking water; Group 2 was fed a "salt free" diet and tap water as drinking water; and Groups 3, 4 and 5 received a "salt free" diet and drinking water containing various

concentrations of NaCl. The resulting chloride intake was 91, 10, 28, 55 and 144 mg/day, respectively. Plasma bromide levels were determined in all rats after 1, 2, 3, 4, 9 and 14 days. Bromide half-lives varied from 2.5 days at high-chloride intake, 3.5 days at normal dietary chloride intake, and 25 days at low-chloride intake (Rauws & van Logten, 1975). It can be concluded that since bromide half-life is about 10 times longer at a low-chloride intake than at the highest chloride intake, the accumulation level in the first case will be about 10 times higher than in the latter case.

The accumulation of bromide was also studied in rat toxicity studies (see "Short-Term Toxicity" section for experimental details). After the administration of normal and low chloride diets, plasma bromide concentrations rose to a plateau within 3 and 12 weeks, respectively. Except for the highest dose groups in both studies, these plateaus were directly proportional to the bromide concentration in the diet. The same levels were reached at bromide concentrations in the low chloride diet, which were about 10 times lower than in the normal chloride diet. In these experiments total halide levels (Cl^- and Br^-) remained the same in the normal diet study and were significantly decreased at the highest dose in the low chloride study only (van Logten et al., 1976; Rauws, 1983).

b. Acute Toxicity

The acute toxicity of bromide in mice and rats is summarized in Table 6. Bromide shows very low acute toxicity following oral administration (FAO/WHO, 1989).

Table 6. Acute Toxicity of Bromide[9]

SPECIES	ROUTE	LD_{50} (mg/kg bw)	REFERENCE
Mouse	Oral	5020	Voss et al. (1961)
Mouse	Oral	7000	Groff et al. (1955)
Rat	Oral	3500	Smith et al (1925)

[9] Table 6 is reproduced from the FAO/WHO (1989) reference. The text was not specific about which salt form of bromide was tested in the 3 studies which appear in Table 6. It is clear from the title of the paper by Smith et al. (1925) that sodium bromide was tested; presumably this was the salt tested in the other two references as sodium is the most common salt, however, this cannot be stated with certainty.

c. Short-Term Toxicity

In a range-finding study, five groups of four female Wistar rats received standard diets or diets containing NaBr (purity 99.5%) at 0, 300, 1200, 4800 or 19200 mg/kg feed for 4 weeks. Animals fed high dose bromide did not groom themselves sufficiently and showed lack of motor coordination in their hind legs. Feeding of a bromide-containing diet did not reveal significant effects on growth, or food or water intake. A dose-related replacement of chloride in plasma and organs by bromide was noted. At the end of three weeks of treatment, plasma bromide concentrations reached a maximum. No compound-related histopathological changes were noted (van Logten et al., 1973a, 1973b).

In another range-finding study, Wistar rats (5/sex/group) were fed NaBr at doses of 0, 75, 300, 1200, 4800 or 19200 mg/kg feed in a low chloride diet (by leaving out NaCl and KCl, but adding 1% potassium sulfate) for 4 weeks. The chloride content of the feed was about 3 g/kg, whereas the normal diet contained 11 g chloride/kg. All rats fed high dose levels died within 12 days, while three male and two female rats in the dosage group of 4800 ppm died within 22 days. At the two highest dose levels food intake and growth were significantly decreased. In male rats in all treatment groups, kidney weight was significantly increased (Kroes et al., 1974).

d. Subchronic Toxicity

In a background document for guidelines for drinking water, WHO (2009) summarized safety studies of bromide. As described in WHO report, Wistar-SPF rats (10/sex/group) were fed low-chloride diets (0.4–0.7 g chloride/kg and 1% potassium sulfate) for 90 days and dosed with NaBr at 0, 8, 31, 125, 500 or 2000 mg/kg feed (purity 99.5%). Body weight and food intake were recorded during the study, and clinical chemistry parameters from blood, urine and liver, bromide and total halide in plasma and several organs, organ weights and histopathology were measured at termination. Three male and three female rats died during the experiment in the highest dose group. In the highest dose group, grooming was depressed, motor incoordination of the hind legs was observed, and body weight gain was significantly decreased. Percentage and total number of neutrophilic granulocytes and the total leukocyte count were increased at the highest dose. A decrease in blood corticosterone levels was noted at the two highest dose levels (significantly at 2000 mg/kg). Additionally in the high dose group, the relative weights of heart, brain, spleen, adrenals, thyroid and pituitary gland were increased in males, whereas the relative prostate weight was decreased. In females receiving 2000 mg NaBr/kg feed, relative heart and brain weights were increased and relative pituitary and uterus weights were decreased. In the two highest dose receiving groups, activation of the thyroid, absence of nephrocalcinosis in female rats, less vacuolization in the zona fasciculata of the adrenals and less zymogen granulae in the pancreas were observed. Fewer corpora lutea, retardation in maturation of the uterus inhibition of spermatogenesis and less secretory activity of the salivary glands were observed in the highest dose groups (van Logten et al., 1976; Rauws et al., 1977).

The results from above-described studies indicate that the highest dose in the low-chloride study (2000 mg/kg) is more toxic (mortality: 6/20) than the highest dose (19200 mg/kg) in the study for rats on a normal diet (mortality 1/20). It appears that the toxicity of NaBr in rats on a low-chloride diet is approximately 10-fold higher compared to that noted in rats on a normal diet.

In another study described in WHO (2009) report, male Wistar rats (10/group/period) were fed diets containing NaBr (purity 99.5%) at 0, 20, 75, 300 or 1200 mg/kg feed for 4 or 12 weeks. Using the same protocol, an additional experiment was completed with sodium bromide at 0 and 19200 mg/kg feed. At the end of 4 and 12 weeks, a significant decrease in body weight was observed in animals fed 19200 mg/kg feed. At the end of 4 weeks, relative thyroid weight was significantly increased in animals fed 1200 mg/kg diet. Similarly, relative thyroid weight was increased at the end of 4 and 12 weeks in animals receiving 19200 mg/kg diet. Microscopic evaluation revealed activation of the thyroid gland and decreased spermatogenesis in the testes in the highest dose group after 4 and 12 weeks. In groups receiving 1200 and 19200 mg/kg diet, thyroxine levels were significantly decreased after 4 weeks and at the highest dose after 12 weeks. A significant increase in thyroid stimulating hormone (TSH) levels was noted at the highest dose after both 4 and 12 weeks. Additionally, insulin levels were significantly increased and growth hormone (GH) (after 12 weeks), testosterone and corticosterone levels were decreased at the high dose level. It was postulated that NaBr acts directly on certain endocrine organs such as thyroid, adrenals and testes, thereby inducing alterations in the pituitary gland feedback mechanisms (Loeber et al., 1983; van Leeuwen et al., 1983). FAO/WHO (1989) also reviewed these reports and determined the no-observed-adverse effect level (NOAEL) of 300 mg/kg diet (equivalent to 240 mg/kg diet as bromide; 12 mg/kg bw/day) for effects on the thyroid.

e. Reproduction

In a three-generation reproductive toxicity study (two litters per generation) described in WHO (2009) report, groups of Wistar rats (10 males and 20 females/group) were fed a diet containing 0, 75, 300, 1200, 4800 or 19200 NaBr mg/kg. Changes in behavior, growth, food and water consumption, leukocyte count and differentiation, triiodothyronine and thyroxine levels in serum, bromide in blood and thyroid, litter size and weight, reproduction parameters, such as fertility, viability and lactation index, organ weights and macroscopic examination were monitored. In animals receiving the highest dose, complete infertility was noted, while at 4800 mg/kg dose, fertility and the viability of the offspring were significantly reduced. In the second and third generations bred only from the groups dosed at up to and including 1200 mg/kg no treatment-related adverse effects were noted in reproductive performance, viability and body weight of the offspring. No clear pattern of dose related effects in the successive generations as measured by body and organ weight measurements were revealed. In F_0 females receiving 4800 and 1200 mg/kg feed, relative adrenal weight was significantly reduced. Reversibility of the observed effects was investigated in an additional litter that was bred with parent animals fed a diet containing 19200 mg NaBr/kg for 7 months followed by a control diet for 3 months before mating. No differences were observed in breeding results between control and exposed rats (van Logten et al., 1979; van Leeuwen et al., 1983). A NOAEL of 300 mg/kg or for bromide ion of 240 mg/kg diet was determined.

f. Mutagenicity

In an Ames test with *Salmonella typhimurium* strains TA98 and TA100, potential mutagenic effects of sodium and ammonium bromide were studied. No mutagenic effects of sodium and ammonium bromide at dose levels of 0.001–10 mg/plate, both with and without metabolic activation, were observed (Voogd, 1988).

4. Human Studies

As a therapeutic agent bromide was once used as an anticonvulsant and a sedative at doses up to 6 g/day (WHO, 2009). Therapeutic uses of bromide have been reported to result in intoxication. Bromide at high doses causes nausea and vomiting, abdominal pain, coma and paralysis. Bromide doses that result in plasma levels of 12 mmol/L (96 mg/L of plasma) produces bromism, and plasma levels greater than 40 mmol/L (320 mg/L of plasma) may cause death (EMEA, 1997). The signs and symptoms of bromide intoxication relate to the nervous system, skin, glandular secretions and gastrointestinal tract (van Leeuwen & Sangster, 1988).

In a clinical study, sodium bromide at a dose of 1 mg/kg bw/day (as bromide) was administered orally to 20 healthy volunteers (10 females not using oral contraceptives and not pregnant and 10 males) for 8 weeks. In this study, female subjects received bromide during two full menstrual cycles. No differences were noted in physical examinations before and after the exposures. Hematological, biochemical and urine parameters also did not show any significant change. An increase in plasma bromide concentrations was noted in females and males from 0.08 ± 0.01 mmol/L to 0.97 ± 0.18 mmol/L and from 0.08 ± 0.01 mmol/L to 0.83 ± 0.09 mmol/L, respectively. Serum concentrations of (Nielsen, 1996) thyroxine, free thyroxine, thyroxine-binding globulin, triiodothyronine, cortisol, testosterone, estradiol or progesterone did not reveal any treatment related changes. Additionally, no changes were noted in the serum concentrations of TSH, prolactin, luteinizing hormone (LH) and follicle stimulating hormone (FSH) measured before as well as 20 and 60 min after the administration of thyrotropin releasing hormone (TRH) and LH releasing hormone (LHRH) (Sangster et al., 1981, 1982a).

In a double blind study, healthy volunteers received sodium bromide at oral bromide doses of 0, 4 or 9 mg/kg bw/day. In this study, groups of seven males received the treatment for 12 weeks, and groups of seven non-pregnant females (not using oral contraceptives) received it over three full estrous cycles. A complete medical history, the results of physical examination, hematological investigations and standard clinical chemistry and urine parameters for each subject were analyzed at the beginning and end of the study. No changes, except for incidental nausea, were observed. At the end of the study, mean plasma bromide concentrations of the 0, 4 and 9 mg/kg bw/day bromide dose groups were 0.07, 2.14 and 4.30 mmol/L for males and 0.07, 3.05 and 4.93 mmol/L for females, respectively. In the females receiving bromide at 9 mg/kg bw/day, a significant increase in serum thyroxine and triiodothyronine at the end compared with pre-administration values was noted, but all concentrations remained within normal limits. Serum concentrations of free thyroxine, thyroxine-binding globulin, cortisol, estradiol, progesterone or testosterone, or of thyrotropin, prolactin, LH and FSH before or after the administration of TRH and LHRH did not reveal any significant changes. Shifts in the power of various spectral bands and a shift in mean frequency in the groups on bromide at 9 mg/kg bw/day as assessed by neurophysiological data (electroencephalogram [EEG] and visual evoked response) was observed, however, all values were within normal limits (Sangster et al., 1982b, 1983). A limited replication study did not show effects on the thyroid or on the central nervous system. Analysis of the EEGs showed only a marginal effect in females receiving bromide at 9 mg/kg bw per day (Sangster et al., 1986).

In a study by van Gelderen et al. (1993), a total of 0, 4 and 9 mg NaBr/kg bw was administered orally to 45 healthy female volunteers. The experiment lasted for six menstrual cycles: only

during the first three cycles was bromide administered. Physical examination and hematological and routine clinical chemistry tests were performed at the start, at the end of the sodium bromide administration period and at the end of the experiment. Except for nausea in relation to the intake of bromide, no adverse effects were observed. By the end of administration period, the bromide concentration in plasma increased to 3.22 ± 0.93 mmol/kg in the 4 mg/kg group and to 7.99 ± 1.89 in the 9 mg/kg group. Before and at the end of the experiment the thyroid hormones (T4, FT4, TBG, T3 and TSH) were analyzed and no significant differences were noted between the groups. Before, after three menstrual cycles, and at the end of the experiment, an EEG with a Visual Evoked Response was recorded. At the 4 and 9 mg/kg dose levels, significant changes were found in the alpha 1-band and the beta-bands. The Visual Evoked Response showed no significant differences between the three groups. From this experiment and previous experiments, the authors proposed a no-effect level in humans for NaBr of 4 mg/kg bw.

5. Opinions in the Scientific & Medical Community about the Safety of Bromide Salts

Inorganic bromide was evaluated by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 1966, and JMPR recommended an acceptable daily intake (ADI) for humans of 0–1 mg/kg body weight, based on a minimum pharmacologically effective dosage in humans of about 900 mg of potassium bromide which is equivalent to 600 mg of bromide. The JMPR ADI of 0–1 mg/kg body weight was reaffirmed with new data in 1989. The monograph also reported a NOAEL for sodium bromide of 300 mg/kg diet (equivalent to 240 mg/kg diet as bromide; 12 mg/kg bw/day) for effects on the thyroid and a NOAEL for neurophysiological or endocrinological changes of 9 mg bromide/kg bw/day (FAO/WHO, 1989).

In 1997, the European Medicines Agency (EMEA, 1997) noted that JMPR took account of the Sangster et al. (1986) human study, but at the time of the JMPR evaluation (FAO/WHO, 1989), the study was provisional and in need of confirmation. Since the JMPR evaluation was first released, the findings have been confirmed in a second human study. A conservative NOEL (for marginal effect within normal limits of EEGs in females at 9 mg/kg bw per day) of 4 mg/kg bw/day (Sangster et al., 1986) suggests an ADI of 0.4 mg/kg bw (EMEA, 1997), including a safety factor of 10 for population diversity.

In 2009, WHO published a background document on bromide in drinking water for development of WHO Guidelines for Drinking-water Quality (WHO, 2009). The WHO recommendations state that the "bromide ion has a low degree of toxicity; thus, bromide is not of toxicological concern in nutrition. Limited findings suggest that bromide may be nutritionally beneficial; for example, insomnia exhibited by some hemodialysis patients has been associated with bromide deficiency (Nielsen, 1996)."

The WHO also states that the ADI of 0.4 mg/kg bw yields an acceptable total daily intake of 24 mg/person for a 60 kg person. Assuming a relative source contribution of 50%, the drinking-water value for a 60 kg adult consuming 2 liters/day would be up to 6 mg/L; for a 10 kg child consuming 1 liter/day, the value would be up to 2 mg/L. However, the dietary bromide contribution for a 10 kg child would probably be less than that for an adult. These are reasonably conservative values, and they are unlikely to be encountered in drinking-water supplies.

VI. DISCUSSION

A. GRAS Criteria

FDA defines "safe" or "safety" as it applies to food ingredients as:

> "...reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance."[10]

Amplification is provided in that the determination of safety is to include probable consumption of the substance in question, the cumulative effect of the substance and appropriate safety factors. It is FDA's operational definition of safety that serves as the framework against which this evaluation is provided.

Furthermore, in discussing GRAS criteria, FDA notes that:

> "...General recognition of safety requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food."
>
> "General recognition of safety through experience based on common use in food prior to January 1, 1958, shall be based solely on food use of the substance prior to January 1, 1958, and shall ordinarily be based upon generally available data and information."[11]

FDA discusses in more detail what is meant by the requirement of general knowledge and acceptance of pertinent information within the scientific community, i.e., the so-called "common knowledge element," in terms of the two following component elements:[12]

- Data and information relied upon to establish safety must be generally available, and this is most commonly established by utilizing published, peer-reviewed scientific journals; and
- There must be a basis to conclude that there is consensus (but not unanimity) among qualified scientists about the safety of the substance for its intended use, and this is established by relying upon secondary scientific literature such as published review articles, textbooks, or compendia, or by obtaining opinions of expert panels or opinions from authoritative bodies, such as JECFA and the National Academy of Sciences.

10 See 21 CFR 170.3(i).
11 See 21 CFR 170.30(a).
12 See Footnote 1.

The apparent imprecision of the terms "appreciable", "at the time" and "reasonable certainty" demonstrates that the FDA recognizes the impossibility of providing absolute safety, in this or any other area (Lu, 1988; Renwick, 1990, Rulis and Leavitt, 2009).

As noted below, this safety assessment to ascertain GRAS status for Salona™ Low Sodium Sea Salt for the defined food uses meets FDA criteria for reasonable certainty of no harm by considering both the technical and common knowledge elements.

B. Discussion of Safety of Salona™ Low Sodium Sea Salt

The Panel has reviewed the manufacturing process, specifications and composition of Salona™ and the regulatory history regarding the safety of potassium chloride and magnesium chloride which are the main components of Salona™. The Panel agrees with the opinions of the scientific and medical communities as stated by SCOGS and IOM on the safety of ingested uses of potassium chloride and magnesium chloride. In addition, safety studies pertaining to the safety of bromine as expressed by WHO were evaluated by the Panel, and the Panel agrees with the opinions regarding safe levels of the bromide in the diet. The Panel agrees with the conclusions of SCOGS, IOM, and Dietary Guidelines for Americans (USDA, 2010) that the projected health benefits of a reduced sodium intake are substantial and would include fewer strokes, cardiovascular disease events, and deaths, as well as substantially reduced health care costs. The use of Salona™ as a salt substitute by both manufacturers of processed foods and consumers would assist in reducing sodium intake.

The Panel has also reviewed the specifications for Salona™ and the associated manufacturing process. Salona™ is manufactured in a HACCP-designed facility in compliance with Good Manufacturing Practices and Food Safety Systems. ICL has established adequate food grade specifications for Salona™.

The Panel agrees that Salona™ has a high presumption of safety because its major components, potassium chloride and magnesium chloride, are both already considered GRAS for uses in foods. Specifically, the IOM did not establish a Tolerable Upper Intake Level (UL) for potassium; therefore, any added potassium resulting from estimated intake of Salona™ does not raise a safety concern. In fact, the added potassium from Salona™ intake may actually be beneficial considering that the IOM report states that dietary intakes of potassium by all groups in the US are considerably lower than the AI of 4.7 g/day for adults older than 18 years of age.

The Panel has determined that the estimated intake of magnesium from Salona™ (319-360 mg/day) is not a safety concern. While these levels are roughly equivalent to the Tolerable Upper Intake Level (UL) for magnesium used as a dietary supplement, it is very unlikely that the intake of magnesium from Salona™ would occur in one single dose (or even 2-4 doses) as it would with dietary supplement usage. The intake of magnesium from the proposed uses can be concluded to be safe because the intake of Salona™ and, in turn, magnesium, would occur slowly over the course of the day and only in the presence of ingested food.

The primary initial symptom from excessive intake of magnesium is diarrhea (IOM, 1997). The laxative effect of magnesium is thought to be osmotically-mediated water retention as a result of high concentrations of magnesium ions that stimulate peristalsis. Magnesium salts are marketed as a laxative at single doses of approximately 1 to 3 g of magnesium. Similar effects due to the ingestion of Salona™ are unlikely because of the low rate of consumption of the magnesium from Salona™ during the day. Additionally, the presence of food in the gastrointestinal tract is likely to counteract the osmotic gradients that underlie the laxative effects seen from high doses such as from a dietary supplement or with a pharmaceutical. The IOM reports states that magnesium ingested as a component of food or food fortificants has not been reported to cause osmotic diarrhea even when large amounts are ingested. The tolerable limit established by IOM for magnesium is intended solely for supplemental magnesium (dietary supplement) and not for food. Patients with chronic renal impairment that are unable to excrete magnesium as successfully are unlikely to experience hypermagnesemia following exposure to magnesium from Salona™ as the increment in total daily magnesium intake will be relatively small.

As the absorption of magnesium decreases with increases in intake (IOM, 1997), any potential adverse systemic effects from elevated blood levels of magnesium are limited by the body's homeostatic mechanisms. Hence, consumption of large doses may be required for the systemic adverse effects associated with hypermagnesemia. Daily doses of magnesium that are 10-fold more than the worst case estimates of consumption are reported to cause systemic effects like metabolic acidosis, hypokalemia, hypotension, and hypoventilation (IOM, 1997). Intended uses of Salona™ are unlikely to result in such high levels of magnesium.

The Panel also notes that Salona™'s intended use is as a salt substitute to reduce sodium levels in foods, which will help offset the safety concerns of IOM and SCOGS pertaining to the excessive levels of sodium in the US diet and help meet the goal of an overall reduction of sodium consumption in the US population. In addition, it is important to note that the substitution of Salona™ will not likely reduce sodium intake to levels below the Adequate Intake (AI) of sodium which is 1.2-1.5 grams per day, depending on age.

The intended use of Salona™ could result in estimated daily maximum intake of 17 mg bromine/day. As described in Section V.D, available *in vitro* animal and human studies support the safety of bromide from the proposed use levels of Salona™. The Panel notes that the estimated levels of bromide from Salona™ usage (17 mg/day/person) are approximately 3-fold lower than the JMPR ADI of 0-1 mg/kg bw (0-60 mg/day for an individual weighing 60 kg), and it is also lower than the EMEA ADI of 0.4 mg/kg bw (24 mg/day). The increase in bromine ion consumption due to the use of Salona™ is unlikely to produce any adverse effects on health.

In addition, as presented, the estimated levels of Salona™ are a worst case scenario. First, the use of Salona™ in food products is self-limiting. Overuse in foods will result in products that have unacceptable taste because most people perceive potassium chloride to taste extremely bitter. The SCOGS had noted that potassium chloride could be substituted for sodium chloride in some of its applications, but they also recognized that the unpleasant taste of substantial amounts of potassium chloride would limit the extent of sodium displacement by potassium. Second, the estimated levels assume 25% substitution of Salona™ for all sources of sodium in foods; this degree of substitution is unlikely considering that sodium in foods comes from other

sources besides NaCl, such as monosodium glutamate, sodium alginate, sodium benzoate, baking soda, baking powder, sodium phosphate and sodium nitrate. Thirdly, it is unlikely that all foods consumed in a given day would have incorporated Salona™ as a partial salt substitute. Considering these factors, it is likely that the maximum daily exposure to Salona would be significantly lower than the estimates calculated in Section IV.B.

Based on the review of the literature and available studies, the Panel concludes that Salona™ Low Sodium Sea Salt is safe for use as a salt substitute as addressed herein.

C. Discussion of Common Knowledge Elements of GRAS Determinations

The first common knowledge element for a GRAS determination is that data and information relied upon to establish safety must be generally available; this is most commonly established by utilizing published, peer-reviewed scientific journals for the safety assessment. The common use of components of Salona™, such as magnesium chloride, potassium chloride and sodium chloride in food on a global basis and the associated absence of harm is based on published information of all types. The majority of the studies reviewed in this safety assessment have been published in the scientific literature as reported in Section V. Additionally, national and international regulatory and other agencies, such as SCOGS, IOM, and WHO, have reviewed the safety of components of Salona™.

The second common knowledge element for a GRAS determination is that there must be consensus among qualified scientists about the safety of the substance with its intended use.

Many competent researchers responsible for the data referred to in this evaluation have expertise in the fields of agriculture, nutrition, toxicology and medicine. They view the components of Salona™ as food ingredients that are viable salt substitutes as well as viable sources of certain nutrients; such substitutions would serve as a means to reduce dietary sodium intake.

The Panel concludes that consensus exists regarding the safety of the intended human food uses of Salona™ based on the following findings:

- Estimated dietary intake of potassium from Salona™ is not a safety concern and actually is likely to be beneficial because dietary intakes of potassium by all groups in the United States are considerably lower than the AI of 4.7 grams;
- Estimated dietary intake of magnesium from Salona™, although potentially equal to the Tolerable Upper Limit for magnesium used as a dietary supplement, will be ingested through the course of the day and not in one dose, as would be the case when used as a dietary supplement;
- Estimated dietary intake of Salona™ will decrease dietary sodium intake and therefore help reduce the risk of various health conditions associated with high sodium intake; in fact, consumption of Salona™ would not present any increased concern with safety; and
- Bromide levels from intake of Salona™ are well below the ADI recommended by the scientific and medical communities.

VII. CONCLUSIONS[13]

The Panel offers the following conclusion:

Salona™ Low Sodium Sea Salt that is produced in accordance with FDA Good Manufacturing Practices requirements and which meets the purity specifications as set forth in Section III.E of this notification, is generally recognized as safe, when consumed in foods at levels up to 4.15 grams per person per day.

This declaration is made in accordance with FDA's standard for food ingredient safety, i.e., reasonable certainty of no harm under the intended conditions of use.

(b) (6)

Richard C. Kraska, Ph.D., DABT

(b) (6)

Robert S. McQuate, Ph.D.

(b) (6)

Madhusudan G. Soni, Ph.D., FACN

September 23, 2011

[13] The detailed educational and professional credentials for two of the individuals serving on the Expert Panel can be found on the GRAS Associates website at www.gras-associates.com. Drs. Kraska and McQuate worked on GRAS and food additive safety issues within FDA's GRAS Review Branch earlier in their careers and subsequently continued working within this area in the private sector. Dr. Soni's curriculum vitae can be accessed at: http://www.soniassociates.net. All three panelists have extensive technical backgrounds in the evaluation of food ingredient safety. Each individual has previously served on multiple GRAS Expert Panels. Dr. Kraska served as Chair of the Panel.

VIII. REFERENCES

Al-Mutaz, I.S., 2000. Water Desalination in the Arabian Gulf Region, in Water Management Purification and Conservation Management in Arid Climates, 245-265. M.F.A. Goosen andW.H. Shayya eds., Boca Raton: CRC Press, pp. 245-265.

Cotton, F.A., Wilkinson, G., 1962. Advanced inorganic chemistry. New York, NY: Interscience Publishers, 441–448.

EMEA, 1997. Bromide, sodium salt. Summary report. London, European Medicines Agency, Committee for Veterinary Medicinal Products. See http://www.emea.europa.eu/pdfs/vet/mrls/018297en.pdf

FAO/WHO, 1989. Bromide ion. In: Pesticide residues in food—1988 evaluations. Part II—Toxicology. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper 93/2. Available at http://www.inchem.org/documents/jmpr/jmpmono/v88pr03.htm

FCC, 2011a. Food Chemicals Codex, Seventh Edition, Supplement 2. Monograph on Magnesium Chloride. The United States Pharmacopeial Convention, Baltimore: United Book Press, Inc.

FCC, 2011b. Food Chemicals Codex, Seventh Edition, Supplement 2. Monograph on Potassium Chloride. The United States Pharmacopeial Convention, Baltimore: United Book Press, Inc.

Federal Register, 1982. HHS (US Department of health and human Services)/FDA. GRAS safety review of sodium chloride; policy notice; solicitation of views. 47 Fed. Reg. (118): 26590—26595.

Ford, E.S., Mokdad, A.H., 2003. Dietary Magnesium Intake in National Sample of U.S. Adults. J. Nutrition, 133:2879-2882.

Goodman, G., 1970. Hypnotics and Sedatives. In The Biological Basis of Therapeutics (4th Ed.). London: MacMillan, 121–2.

Groff, F., Tripod, J., Meyer, R., 1955. Zur pharmakologischen karakterisierung des Schlafmittels Doriden. Schweiz. med. wschr., 85, 305.

IOM, 1997. Institute of Medicine. Dietary Reference Intakes for Calcium Phosphorus, Magnesium, Vitamin D and Flouride. Available at http://books.nap.edu/openbook.php?record_id=5776&page=1.

IOM, 2005. Institute of Medicine. Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate. Available at http://www.nap.edu/openbook.php?record_id=10925&page=1.

IOM, 2010. Institute of Medicine. Committee on Strategies to Reduce Sodium Intake. Strategies to Reduce Sodium Intake in the United States. Eds.: Henney, J.E., Taylor, C.L., Boon, C.S. Washington (DC). National Academies Press.

JECFA, 2006. Joint FAO/WHO Expert Committee on Food Additives. Combined Compendium of Food Additive Specifications. Food and Agriculture Organizations of the United Nations. Rome, Italy.

King, D.E., Mainous, A.G., Geesey, M.E., Woolson, F.W., 2005. Dietary magnesium and C-reactive protein levels. J. Am. Coll. Nutr., 24:166-171.

Kroes, R., Rauws, A.G., Verhoef, C.H., de Vries, T. & Berkvens, J.M., 1974. Oriënterend toxiciteits onderzoek van het bromide-ion in chloride-arm dieet bij de rat. Report nr. 187 Tox. d.d. december from Rijks Instituut voor de olksgezondheid. Submitted to WHO by RIVM, Bilthoven, Holland.

Loeber, J.G., Franken, M.A.M., van Leeuwen, F.X.R., 1983. Effect of sodium bromide on endocrine parameters in the rat as studied by immunocytochemistry and radioimmunoassay. Food and Chemical Toxicology, 21(4):391–404.

Lu, F.C., 1988. Acceptable daily intake: inception, evolution and application. Regul. Toxicol.Pharmacol. 8, 45-60.

Mattes, R.D., Donnelly, D., 1991. Relative contributions of dietary sodium sources. J Am Coll Nutr, 10(4):383-93.

Nielsen, F.H., 1996. Other Trace Elements. In: Present Knowledge in Nutrition (Ziegler, E.E. and Filer, L.J.Jr., eds.), 7th Edition, pp. 353-377. International Life Sciences Institute Press. Washington, DC.

NHANES III, 1988-1994. U.S. Department of Health and Human Services. National Center for Health Statistics. Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

Rauws, A.G., van Logten, M.J., 1975. The influence on dietary chloride on bromide excretion in the rat. Toxicology, 3, 29-32.

Rauws, A.G., et al., (additional authors unknown), 1977. Onderzoek naar de semichronische toxiciteit van bet bromide-ion bij ratten op zoutarm dieet. Submitted to WHO by Rijksinstituut voor de volksgezondheid, Bilthoven, August (Report No. 180/77 Alg Tox).

Rauws, A.G., 1983. Pharmacokinetics of bromide ion-an overview. Food Chem. Tox. 21:379-382.

Renwick, A.G., 1990. Acceptable daily intake and the regulation of intense sweeteners. Food Addt. Contam. 7, 463-75.

Rulis, A.M., Levitt, J.A., 2009. FDA's food ingredient approval process: Safety assurance based on scientific assessment. Reg Tox Pharm 53, 20-31.

Sangster, B., et al. (additional authors unknown), 1981. Onderzoek naar de invloed van natriumbromide bij menselijke vrijwilligers. d.d. Utrecht/Bilthoven. Rijksinstituut voor de volksgezondheid. February (Report No. 167/80 617911001 NVIC/Alg Tox/Endo/Farmkin/KCEH).

Sangster, B., Krajnc, E.I., Loeber, J.G., Rauws, A.G., van Logten, M.J., 1982a. Study of sodium bromide in human volunteers, with special emphasis on the endocrine system. Human Toxicology, 1:393–402.

Sangster, B., et al. (additional authors unknown), 1982b. Onderzoek naar de invloed van natriumbromide bij menseltjke vrijwilligers: II. Bilthoven. Rijksinstituut voor de volksgezondheid. November (Report No. 348002001).

Sangster, B., Blom, J.L., Sekhuis, V.M., Loeber, J.G., Rauws, A.G., Koedam, J.C., Kranjc, E.I., van Logten, M.J., 1983. The influence of sodium bromide in man: a study in human volunteers with special emphasis on the endocrine and the central nervous system. Food and Chemical Toxicology, 21(4):409–419.

Sangster, B., et al. (additional authors unknown), 1986. Onderzoek naar de invloed van natriumbromide bij menselijke vrijwilligers: III. Bilthoven. Rijksinstituut voor de volksgezondheid en milieuhygiene (RIVM). October (Report No. 348301001).

SCOGS, 1976. Select Committee on GRAS Substances. Evaluation of the Health Aspects of Magnesium Salts as Food Ingredients. Report No. 60.

SCOGS, 1979. Select Committee on GRAS Substances. Evaluation of the Health Aspects of Sodium chloride and Potassium Chloride as Food Ingredients. Report No. 102.

Smith, P.K., Hambourger, W.E., 1925. Antipyretic toxic effects of combinations of acetanilide with sodium bromide and with caffeine. Journal of Pharmacology and Experimental Therapeutics, 55:200 [cited in van Leeuwen, den Tonkelaar & van Logten, 1983].

Söremark, A, Ullberg, S., 1960. Distribution of bromide in mice. An autoradiographic study with 82Br. Intern. J. Appl. Rad. Isot., 8, 192-197.

USDA, 2010. Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2010. http://www.cnpp.usda.gov/Publications/Dietary Guidelines/2010/DGAC/Report/2010DGACReport-camera-ready-Jan11-11.pdf.

van Gelderen, C.E.,Savelkoul T.J., Blom, J.L., van Dokkum, W., Kroes, R., 1993. The no-effect level of sodium bromide in healthy volunteers. Hum Exp Toxicol.12(1):9-14.

van Leeuwen, F.X.R., Sangster, B.,1988. The toxicology of bromide ion. CRC Critical Reviews in Toxicology, 18(3):189–215.

van Leeuwen, F.X.R., den Tonkelaar, E.M., van Logten, M.J., 1983. Toxicity of sodium bromide in rats: effects on endocrine system and reproduction. Food and Chemical Toxicology, 21(4):383–390.

van Logten, M.J., Wolthuis, M., Rauws, A.G., Kroes, R.,1973a. Range-finding onderzoek naar de toxiciteit van her bromide-ion bij de rat. Submitted to WHO by Rijksinstituut voor de volksgezondheid, Bilthoven. (Report No. 70/73 Tox).

van Logten, M.J., Wolthuis, M., Rauws, A.G. & Kroes, R., 1973b. Short-term toxicity study on sodium bromide in rats. Toxicology, 1:321-327.

van Logten, M.J., Rauws, A.G., Kroes, R., den Tonkelaar, E.M. & van Esch, G.J., 1976. Semichronic toxicity studies of sodium bromide in rats on a normal diet and a low chloride diet. Med. fac. landbouw. Rijksuniv. Gent, 41/2, 1499-1507.

van Logten, M.J., Rauws, A.G., Bremmer, J.N., van Leeuwen, F.X.R., de Liefde, T., Peters, P.W.J., 1979. reproductieproef met natriumbromide bij ratten. Interim-rapport Alg Tox/Farm/Path january/79 from Rijksinstituut voor de volksgezondheid, Bilthoven, Holland.

Voogd, C.E., 1988. Personal communication [cited in FAO/WHO, 1989].

Voss, E., Haskel, A.R., Gartenberg, L., 1961. Reduction of tetremicine toxicity by sedatives and anticonvulsants. J. Pharm. Sci., 50, 305. Cited in van Leeuwen, et al., 1983.

WHO, 2009. Bromide in Drinking Water: background document for development of WHO Guidelines for Drinking Water Quality. World Health Organization. Available at: http://whqlibdoc.who.int/hq/2009/WHO_HSE_WSH_09.01_6_eng.pdf.

APPENDIX A

Salona™ Certificates of Analysis

Certificates of Analysis
Salona™ (Low Sodium Sea Salt)

Lot #	Specification	09252001-10F	09252001-15F	09252001-17F	09252001-11M	09252001-13M	09252001-18M
Magnesium Chloride, $MgCl_2$, %	**31 – 35**	33.4	33.0	33.9	32.8	32.8	32.7
Potassium Chloride, KCl, %	**21 – 26**	23.3	23.4	24.3	23.9	23.5	24.2
Sodium Chloride, NaCl, %	**< 7**	4.5	5.3	4.1	4.6	5.2	4.5
Bromide, Br, %	**< 0.4**	0.37	0.37	0.37	0.37	0.37	0.36
Total Organic Carbon, mg/kg*	**< 10**	< 10	< 10	< 10	< 10	< 10	< 10
Heavy Metals as lead (Pb), mg/kg	**< 10**	< 10	< 10	< 10	< 10	< 10	< 10
Lead, Pb, mg/kg	**< 2**	< 2	< 2	< 2	< 2	< 2	< 2
Water Insolubles, %	**< 0.1**	0.02	0.02	0.03	0.02	0.03	0.01
Sizing, USSS							
Retained on a 20 Mesh, %	**< 15**	15.1	13.6	5.5			
Retained on a 12 Mesh, %	**< 10**				6.4	11.4	7.3

Lot #	Specification	09252001-12C	09252001-14C	09252001-16C
Magnesium Chloride, $MgCl_2$, %	**31 – 35**	33.0	33.0	34.1
Potassium Chloride, KCl, %	**21 – 26**	24.9	24.8	24.8
Sodium Chloride, NaCl, %	**< 7**	2.7	3.6	4.6
Bromide, Br, %	**< 0.4**	0.37	0.37	0.38
Total Organic Carbon, mg/kg*	**< 10**	< 10	< 10	< 10
Heavy Metals as lead (Pb), mg/kg	**< 10**	< 10	< 10	< 10
Lead, Pb, mg/kg	**< 2**	< 2	< 2	< 2
Water Insolubles, %	**< 0.1**	0.01	0.01	0.01
Sizing, USSS				
Retained on a 16 Mesh, %	**> 90**	99.9	99.4	99.2

* guaranteed

SUBMISSION END